Chapter 8

The Prototype Development

8.1 Introduction

The challenge in the design of an innovative hypothermic human liver perfusion system is to incorporate optimal perfusion dynamics and sufficient oxygenation at hypothermic temperature, as major requirements defined in Chapter 6, in a portable, affordable and userfriendly system.
The best estimation of the required amount of perfusion of the liver using hypothermic machine perfusion (HMP) can be derived from physiology data, using in-situ an hepatic artery pulsatile flow and for the portal vein a non-pulsatile flow. One of the major advantages of continuous machine perfusion is the ability to monitor perfusion characteristics throughout preservation. Values and trends in pressure and flow patterns, as well as subsequently organ vascular resistance, can be used to determine their relation with organ viability after preservation. For example, in kidney HMP intra renal resistance (IRR) is frequently used as an indicator of preservation quality and organ viability as increased IRR is due to cell swelling and tissue edema.
Hypothermia results in vasoconstriction of blood vessels in the liver and renders endothelial cells fragile and more prone to shear stress induced injury (Chapter 6). Pressure control is therefore essential to prevent the injury of the vessel wall and endothelial cell as a result from a too high perfusion. By controlling perfusion pressure, flow becomes dependent of liver vascular resistance (Poisseuille's law) and either can never get too high. Thus using pressure-controlled devices, shear stress in the vessels can never get too high and endothelial cell damage is prevented. In hypothermic machine perfusion of kidneys it has been demonstrated that the re-

sistance to flow will vary during perfusion. Some authors have reported decreased IRR of up to 48% during pulsatile renal perfusion for 10 hours and longer[3,4]. Since this resistance variation during machine perfusion could occur in the liver as well, it is also of importance to measure and control the pump pressure.
Furthermore, despite the fact that hypothermia decreases cellular metabolism, the liver still consumes oxygen during hypothermic machine preservation[1], suggesting that additional oxygen is mandatory during perfusion to achieve optimal preservation of the liver.
Another important requirement for a liver HMP system is a stand-alone working period of at least 24 hours, implying a cooling capacity to maintain hypothermic conditions within the range of 0 to 4°C for 24 hours. Furthermore, for detection of increasing temperatures, a temperature sensor is needed to monitor organ and preservation solution temperature.
In addition, it is mandatory for successful use and implementation of HMP for the liver that the HMP system is compatible with the standard operating procedures surgeons use during organ procurement. The static cold storage technique is currently the golden standard for liver and should be the departure for the design of a HMP system. A new system should incorporate equivalent handling, surgical procedures and materials, with the addition of a simple dual pumping system. Furthermore, such a system should be portable to allow easy transportation and preferably be disposable, at least in part. For this purpose, according to NIOSH lifting regulations a weight of 23 kg or less is the target[6]. At last, the HMP system should be a low-cost system to fit in hospital budgets and be reembursed by insurance companies.
Applying the above described technical requirements, we defined the functional scheme of the Groningen HMP system as shown in Figure 8.1. The following paragraphs address the different components of the HMP system including pumps, oxygenator, sensors and controller. Subsequently, the design integrating these components and the additional requirements into the first prototype will be described.

8.2 Pumps

The continuous pump (PV pump) should be able to generate a portal venous pressure of 4 mmHg, while for the pulsatile pump (HA pump) hepatic arterial pressures of 30/20 mmHg should be possible. Based on experiences with kidney HMP, we defined the working pressure range for the continuous pump as: 4-12

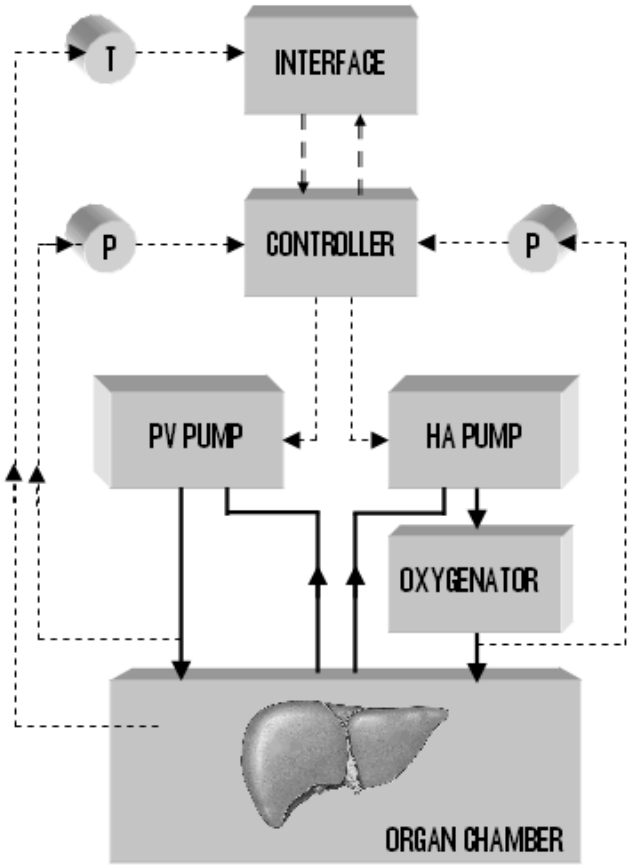

Figure 8.1: Functional scheme of the Groningen HMP system, including interface, controller, pressure sensors (P), temperature sensor (T), portal (PV) and arterial (HA) pump, oxygenator and organ chamber.

mmHg, and for the pulsatile arterial pump: 30/20-120/80 mmHg, where 12 mmHg and 120/80 mmHg are the corresponding physiologic values. In addition, pulsatile pressure is aplied as a sinusoidal pulse, with a frequency of 1 Hz. Additional selection criteria for the pumps included low energy consumption, light-weight small-size, operable in hypothermic conditions, affordable and ease-of-use.

Basically, there are two main blood pump types, i.e. positive displacement pumps and rotary pumps. Displacement pumps include roller pumps, membrane pumps and piston pumps, and are based on the principle of pushing fluid forwards.

- A roller pump uses two or more rollers that accomplish a peristaltic movement by squeezing a tube containing fluid alternately. Depending on the number of rollers, the resulting flow is pulsatile or near-continuous.
- A membrane pump consists of a flexible membrane that separates the fluid from a driving medium, in most cases compressed air. The driving volume alternately moves the membrane up and down, and subsequently the fluid is forced in and out the membrane pump. As a consequence, the membrane pump is a purely pulsatile pump. Uni-directional flow can be obtained by the use of in and out flow valves.
- The piston pump uses the same principle as the membrane pump, differing from it as that a rigid membrane forces the fluid in and out of the pump, and that in most cases, instead of a driving medium, a screw spindle is the driving force. The advantage of the piston technique is that the fluid displacement is larger than in the membrane pump, which is limited due to the displacement of the membrane. A well known example of a piston pump is the syringe pump.
- Rotary pumps are based on the accelerating free flow of fluids, by means of an impeller. Depending on the shape and orientation of the vanes of the impeller, a rotary pump can be a purely centrifugal, radial (e.g. irrigation pump), axial (e.g. propulsion screw of a ship) or combinations of these (mixed flow pumps). The major difference between rotary pumps and displacement pumps is that displacement pumps by definition are flow controlled pumps, while rotary pumps are more pressure controlled pumps.

	Displacement			Rotary
	Roller	Membrane	Piston	
Pulse	++	++	++	+
Continuous	+/-	–	–	++
Efficiency	-	+	+/-	++
Weight	+/-	+	+	++
Dimension	+	+	++	++
Hypothermia	+/-	+/-	+	++
Ease-of-use	++	+/-	++	++

Table 8.1: Scores of the different pumps on the selection criteria.

The different types of pumps are compared in Table 8.1 and scored according to their compliance with our selection criteria. The roller pump is able to generate pulsating flow and, depending on the number of rollers, a more or less continuous flow. By definition, a roller pump, however, is not efficient, because it has to deform tubing to push the fluid forward. Consequently, a powerful motor and stiff construction make the pump heavy and bulky. Moreover, during hypothermia, the tubing stiffness increases, making the pump even more inefficient. However, the ease-of-use of a roller pump is excellent since it implies that only the tubing has to be put around the rollers. A membrane pump, by definition, is a pulsatile pump with no possibility to generate a continuous flow. Efficiency, weight, dimension and ease-of-use depend strongly on the driving medium. Hypothermia further slightly affects the stiffness of the membrane which influences efficiency. The piston pump principle is comparable with the membrane pump. An electromotor-driven screw spindle makes smaller dimensions possible with an increased ease-of-use. At last, rotary pumps are mainly continuous flow pumps, but by driving them at alternating speeds, a pulsatile flow can be obtained. They are energy efficient by minimization of friction and consequently can be constructed light and small. Hypothermia does not affect the pump and the userfriendlyness is good.
For the application in the Groningen Portable Hypothermic Liver Perfusion System, it was of major importance that the pumps could work in a continuous as well as a pulsatile mode and had a low energy consumption. For that reason, we decided to choose the rotary pump principle. In this way it was possible to use both for the pulsatile as well as the continuous flow the same pump. An additional advantage of this principle is that in case of a possible increased resistance or even occlusion the rotary pump is not able to generate enormous pressures, since it just accelerates free flow. Consequently, possible tissue damage due to too high pressures is prevented.

8.2.1 DeltaStream

For application in the Groningen HMP System, a commercially available rotary pump was selected. The DeltaStream DP2 rotary pump was developed at the Helmholtz-Institute for BioMedical Technology (Aachen, Germany) and is now manufactured and distributed by MEDOS Medizintechnik AG (Stolberg, Germany). The DeltaStream rotary pump was originally developed as a miniaturized blood pump to be applied in cardiopulmonary bypass, extracorporeal life support or as ventricular assist device. The DeltaStream basically consists of an electromotor, and a disposable pump head (Figure 2). Main advantages of the DeltaStream DP2 include disposable pump head, easy click-on system, easy control system and the possibility of both pulsatile as well as continuous flow.

Figure 8.2: The DeltaStream DP2 rotary blood pump, with the electromotor (left) and disposable pump head (right).

The electromotor is a 12V, 50W DC motor (EC 22, Maxon Motor, Sachseln, Switzerland) and is provided with heat sinks for cooling. This motor is a brushless electric motor, which has the advantage that the life-time is much higher than that of a conventional electromotor. Instead of brushes, this motor is provided with 3 so-called Hall-sensors, which determine the position of the rotor. This position, on its turn, determines the route of electric current through the windings. As a consequence, a controlling unit (1-Q-EC, Maxon Motor, Sachseln, Switzerland) is necessary to read out the Hall-sensors and control the route of current. In this controlling unit, also a motor velocity control loop (PI-controller, see § 8.5) is in-

corporated.
The disposable pump head consists of an impeller fitted in a housing containing an axial inlet and a radial outlet (Figure 8.2). The geometry of the impeller is developed in such a way that it combines the advantage of a purely radial impeller (high pressure build-up) and a purely axial impeller (high capacity, small dimension) in a so-called mixed-flow design. The disposable pump head is coupled to the electromotor by means of a magnetic coupling mechanism. On the axis of the motor 4 magnets are present, which couple with 4 metal plates on the axis of the impeller.
In the standard DeltaStream cardiopulmonary bypass, pumping 37°C blood, this configuration is able to produce a pressure difference over the pump of 0-600 mmHg with a flow range of 0-8 l/min. The rotational speed of the impeller ranges in that case from 100-10000 RPM.
For application in the Groningen HMP System, the DeltaStream pump should

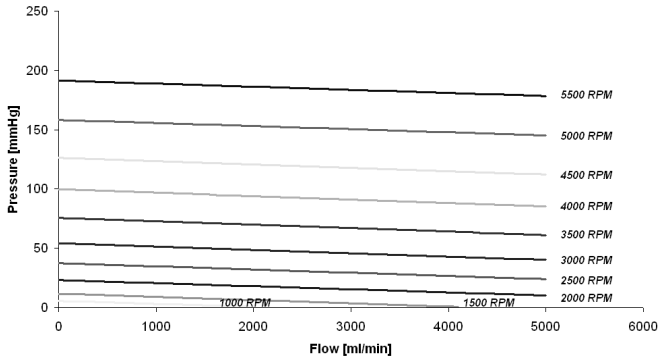

Figure 8.3: The pump characteristics of the DeltaStream DP2 rotary blood pump using 0-4°C UW-MP.

be able to work under hypothermic conditions (0-4°) with UW-MP preservation solution instead of blood. The low temperature and the different medium result in an increased viscosity compared to normothermic blood[5], and thus the pump characteristics of the DeltaStream are altered. To study if the DeltaStream is applicable in HMP, we measured the pump characteristics, defined by the relation between the pressure difference, resulting flow and rotational speed of the impeller using UW-MP at hypothermic conditions (Figure 8.3).

As can be seen in Figure 8.3, with rotational speeds of 5500 RPM, a pressure head of 190 mmHg with resulting flows of 5 l/min was achieved. In our HMP

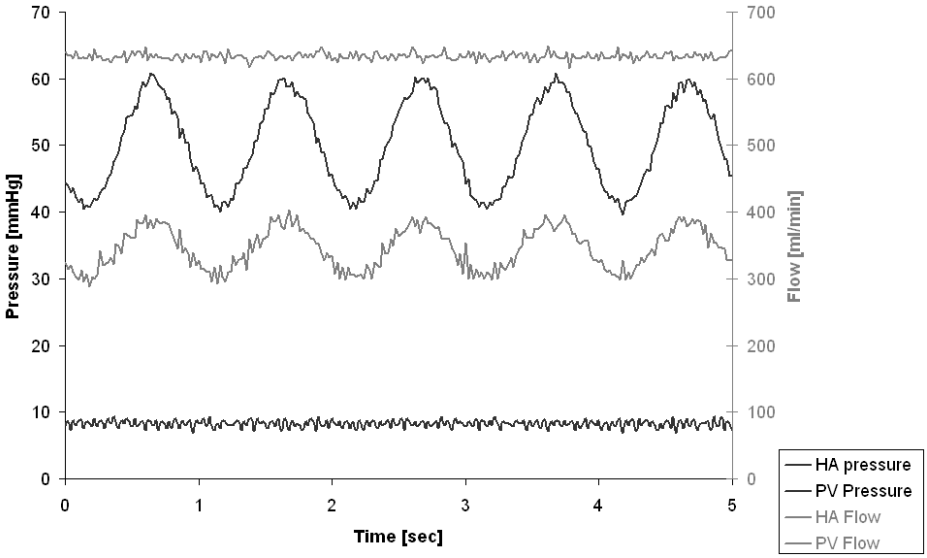

Figure 8.4: Pulsatile as well as continuous pumping mode of the DeltaStream DP2.

setting the perfusion pressure was defined as 4 mmHg for the continuous line and 30/20 mmHg for the pulsatile line. From the results illustrated in Figure 8.3 it was concluded that these settings could be easily achieved with the DeltaStream pump, and were even in the lower operating region of the overall pump characteristics. To generate a pulsatile perfusion, the electromotor could be driven using a sinusoidal current pattern, resulting in an alternately accelerating and decelerating impeller and thus a pulsatile flow (Figure 8.4).

In summary, the DeltaStream rotary pump appeared to be the most suitable pump system for application in the Groningen Portable Hypothermic Liver Perfusion System. Under hypothermic conditions using UW-MP, it is possible to generate the necessary pulsatile as well as continuous pressure and flow, and has as advantage that pressure build up will never be at very high levels, preventing possible tissue damage. Furthermore, the DeltaStream is energy efficient, light-weigth, easy-to-handle because of its disposable pump head, has small dimensions and is affordable.

8.3 Oxygenator

To supply the liver with a sufficient amount of oxygen during HMP, the HILITE 800LT oxygenator (Medos Medizintechnik Ag, Stolberg, Germany) was selected as best out of four tested types of miniature oxygenators (see Chapter 7). The HILITE 800LT oxygenator is a hollow fiber membrane oxygenator comprising plasma-tight coated fibers that make it suitable for long term use. Oxygenation capacity of the HILITE was 70-90 kPa for fluid flow rates of 250-1000 ml/min, respectively, which is sufficient to fulfill the hypothermic liver's oxygen demand. At these flow rates, pressure drop was 12.8-69.3 mmHg, which was the lowest of the four tested oxygenators. Small dimensions and affordable costs make this oxygenator optimal for application in the Groningen HMP system.

8.4 Sensors

8.4.1 Pressure

The pressure at which the liver is perfused is defined as the pressure the pump generates, measured near the entrances of the liver (hepatic arterial canula and portal venous canula), with outside air as reference. Expected pressures to be measured with an accuracy of 1 mmHg were for the continuous line 4 mmHg and for the pulsatile line 30/20 mmHg. However, to monitor the entire working range as defined at the beginning of this chapter, expected pressure could rise to 12 mmHg (continuous) and 120 mmHg (pulsatile). In addition, the pressure transducer should be able to operate under hypothermic conditions and be preferably disposable.
We selected the TruWave disposable blood pressure transducer (Edwards Lifesciences, Irvine, USA) (Figure 8.5) to measure the pressure in the HMP system. This transducer is already incorporated in a housing, making application easy and the sensor is already widely used in hospitals around the world. The specifications of this pressure transducer include an operating range of -50 to 300 mmHg within a temperature range of 15 to 40°C and a zero offset of ±25 mmHg. The Truwave pressure transducer consists of a membrane that measures the difference between the fluid pressure and the ambient air pressure. Consequently, the transducer has to be zeroed at air pressure before measurement to counteract the zero offset. Due to the temperature operating range of 15-40°C, which aswers to the international standard for disposable pressure transducers (ANSI/AAMI BP22:1994), meaning that all specifications are guaranteed in this temperature range, the pressure sensors

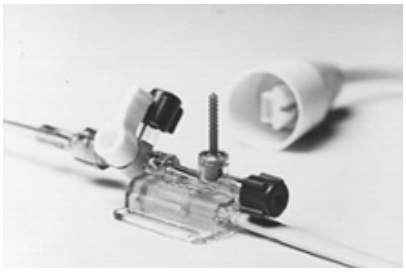

Figure 8.5: The Truwave sterile disposable pressure transducer.

have to be placed outside the cooling box. Although the UW-MP circulating inside the cooling box is at 0-4°C, placing the sensors outside results in equilibration of the stagnant UW-MP in the pressure measurement tube with room temperature, and specifications are guaranteed. In this configuration the transducer is applicable in our HMP system with an accuracy of 4 mmHg. It is important to realize that this accuracy is a theoretical worst case scenario. In our experiences, the accuracy was high enough to detect pressures as low as 4 mmHg.
With this pressure sensor, we are able to measure perfusion pressure and subsequently control this pressure, detect kinked or loosened tubing and calculate, in combination with perfusion flow, organ vascular resistance as a measure of organ viability.

8.4.2 Flow

To determine and analyze perfusion flow patterns, flow has to be measured as well. Several concepts for flow measurements exist, based on laser doppler, thermal mass flow, transit-time ultrasound or number of turbine rotations. For application within the perfusion pump, these concepts had disadvantages in type of fluid, perfusate temperature rise, costs and high pressure drop, respectively. Therefore, another principle was adapted to measure the perfusion flow in the hypothermic perfusion pump. Since electro-motors were used to drive the centrifugal pump heads, the rotational speed [rpm] of the motors could be used as a measure for perfusion flow. However, the rotational speed depends of the perfusion pressure as well (Figure 8.3). Provided that the perfusion pressure remains constant, which is achieved by a controller (see § 8.5), the rotational speed of the pump motors can theoretically be used as a measure of perfusion flow.
This measurement principle was validated by comparing perfusion flow in the HMP

system measured with an ultrasound transit-time flow probe (H7C, Transonic Systems, Ithaca USA) and the rotational speed of the two centrifugal pumps.

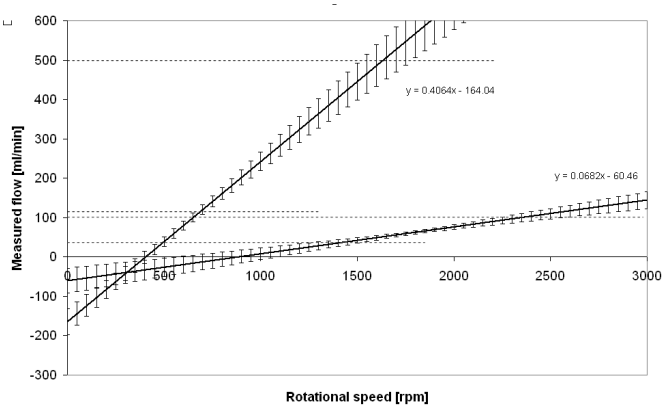

Figure 8.6: Measured perfusion flow as a function of rotational speed of the pumps (mean ± sd).

Validation was performed with pig livers (n=5) at 0-4°C. Perfusion pressure was kept constant at 4 mmHg for the continuous pump and 30/20 mmHg for the arterial pump.
As a result, Figure 8.6 shows the measured perfusion flow [ml/min] as a function of the rotational speed [rpm]. For both the arterial and portal venous line this can be fitted to a linear relation:

$$Flow_{HA} = 0.0682 \cdot rpm - 60.46 \tag{8.1}$$

and

$$Flow_{PV} = 0.4064 \cdot rpm - 164.04 \tag{8.2}$$

Expected flow rates for the hepatic artery are between 40 and 100 ml/min, for the portal vein between 100 and 500 ml/min. Flow determination using equations 8.1 and 8.2 in the expected flow range results in a maximum error of 14% and 17% respectively.
To monitor changes in organ vascular resistance as an indicator of organ viability, these errors are well acceptable, because the accuracy is high enough to determine any trouble shooting during perfusion, e.g. loose or obstructed tubing.

8.4.3 Temperature

The HMP system operates at hypothermic temperature (0-4°C) which has to be maintained throughout the entire preservation period. A sensor that registers the temperature of the liver in the cooling box should be able to measure a temperature range from -5 to 40°C with an accuracy of 0.5°C, to keep options open for future alternative higher operating temperatures. Furthermore, the sensor should be waterproof, disposable and operable without calibration.
Several types of sensors are currently available, including thermocouples, temperature sensor IC's and thermistors. Thermocouples have the disadvantage that calibration before measurement is always required. Temperature IC's are generally expensive and hard to be made waterproof. Therefore, for application in our HMP system, we selected a thermistor temperature sensor (BetaTHERM, Galway, Ireland). The BetaTHEM thermistor has an accuracy of 0.2°C within a temperature range from -10 to 40°C. In combination with electronics and software accuracy, a total temperature measurement accuracy of 0.5°C is feasible. The thermistor and its extension cable are coated for protection against water and moisture.

8.5 Controller

To keep the set perfusion pressure of the continuous portal venous pump and the pulsatile hepatic arterial pump at a constant level independent of liver resistance, a proportional integral derivative (PID) controller was implemented. A controller compares the perfusion pressure that is preset by the user with the actual perfusion pressure. If difference occurs between these parameters, the controller adapts the rotational speed of the pump motor to make that difference as small as possible. A PID controller is characterized by a proportional part (Pp), an integral part (Pi) and a derivative part (Pd) (Figure 8.7).

The proportional parameter changes the perfusion pressure in proportion to the error (ε), which is defined as the difference between the Set Perfusion Pressure (SPP) and the Measured Perfusion Pressure (MPP). The control action is proportional to both Pp and ε; a higher Pp as well as a larger error will increase the amount of control action. In addition to this proportional change, the integral parameter produces a time-dependent correction of the perfusion pressure, resulting in a minimized ε. Finally, the derivative control action depends on the rate of change of the error, and benefits making the controller respond faster.
In the liver perfusion system, three separate controllers are necessary to control the

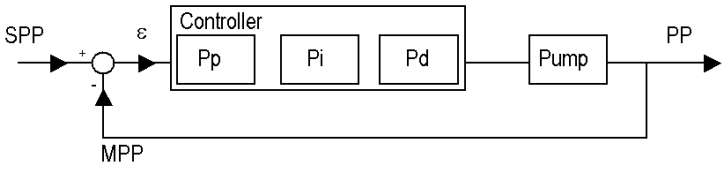

Figure 8.7: PID controller. (SPP=Set Perfusion Pressure, PP=Perfusion Pressure, MPP=Measured Perfusion Pressure, ε=error)

continuous portal venous perfusion pressure, the mean and the amplitude of the pulsatile hepatic arterial perfusion pressure. In this paragraph we present the optimal parameters of these three controllers and illustrate the function of the controllers using optimal parameters.

8.5.1 Algorithm

Three PID controllers were implemented in the measurement and control software (Labview 5.1, National Instruments, Austin (Texas), USA), one to control the continuous pressure of the portal venous branch, and two to control the mean and amplitude of the pulsatile pressure of the hepatic arterial branch. For each PID controller the values Pp, Pi and Pd were set separately.
The output u of a PID controller at time t is given by (8.3):

$$u(t) = Pp\varepsilon(t) + Pi\int_0^t \varepsilon(t)dt + Pd\frac{d\varepsilon(t)}{dt} + u_0 \tag{8.3}$$

with $\varepsilon(t)$ the error signal at time t, calculated as the difference between the measured pressure and the set pressure. Discretisation using:

$$\frac{d\varepsilon(t)}{dt} \approx \frac{\varepsilon(n) - \varepsilon(n-1)}{T_s} \tag{8.4}$$

and:

$$\int_0^t \varepsilon(t)dt \approx T_s\sum_0^n \varepsilon(i) \tag{8.5}$$

with T_s the sample time, gives the discrete PID algorithm:

$$u(n) = Pp\varepsilon(n) + PiT_s \sum_{0}^{n} \varepsilon(i) + Pd\frac{\varepsilon(n) - \varepsilon(n-1)}{T_s} + u_0 \tag{8.6}$$

This PID algorithm is called a positional PID controller because of the use of a base level u_0. Subtraction of (8.6) for $u(n-1)$ from $u(n)$ gives the velocity PID control algorithm:

$$u(n) = u(n-1) + Pp[\varepsilon(n) - \varepsilon(n-1)] + PiT_s\varepsilon(n) + Pd\frac{\varepsilon(n) - 2\varepsilon(n-1) + \varepsilon(n-2)}{T_s} \tag{8.7}$$

Since in our system u_0 is unknown, this is the algorithm to use in the PID pressure controller in the HMP system. Continuous control is performed every cycle of the control loop, pulsatile control only every number of samples per sinusoidal period, since one full period is needed to determine mean and amplitude and consequently $\varepsilon(n)$. The experiments were performed with 10 samples per period, meaning that pulsatile control is active every 10^{th} cycle.

8.5.2 Parameter setting

To determine the optimal settings of the PID parameters of the controllers for continuous pressure and for mean and amplitude of pulsatile pressure, they were subjected to trial-and-error testing. The experimental set-up (Figure 8.8) consists of a reservoir with HES-solution with a similar viscosity as UW-MP, a continuous (PV) and a pulsatile (HA) pump (Deltastream DP2, Medos Medizintechnik AG, Stolberg, Germany), an oxygenator in the arterial line (HILITE 800LT, Medos Medizintechnik AG, Stolberg, Germany), two flow probes (Q) (H7C, Transonic Systems Inc, Ithaca, USA), two pressure sensors (P) (Truwave, Edwards Lifesciences, Irvine, USA) and two variable resistances (R). The whole set-up was kept at 0°C by cooling with ice.

The variable resistance in the portal venous line was set in such a way that with a pressure of 8 mmHg the resulting flow was 300 ml/min, the hepatic arterial resistance in a way that a pulsatile pressure of 60/40 mmHg, 1 Hz, resulted in a mean flow of 100 ml/min. Using these settings of the resistances, the SPP was set at 4 mmHg for the continuous portal venous line and 25 mmHg and 5 mmHg as mean and amplitude for the pulsatile hepatic arterial line[2]. The performance of the three controllers was analyzed by varying the three PID parameters one at a time. Optimal settings were defined for a total control reaction time of 1 minute. To

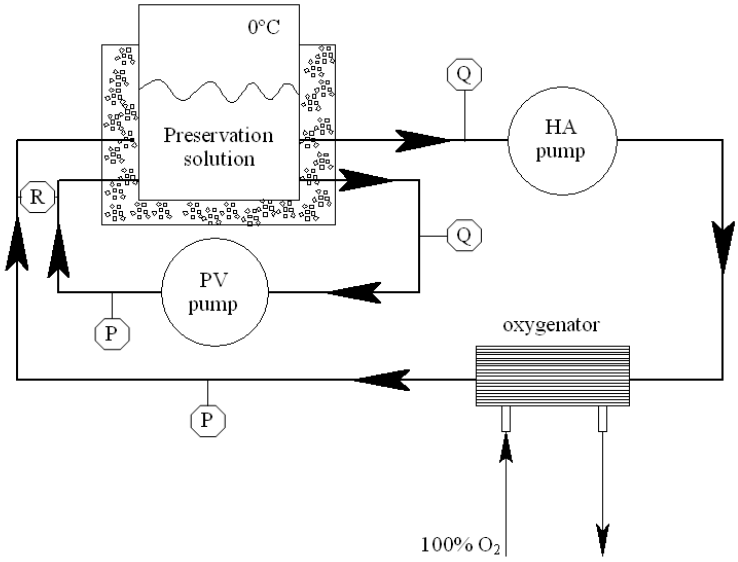

Figure 8.8: Experimental set-up.

determine stability of perfusion pressure compared to the SPP, standard deviation of perfusion pressure [mmHg] and control signal (motor steering signal) [rpm] was calculated as well.

Portal venous control

The set perfusion pressure (SPP) was set at 4 mmHg. First, the Pi_{PV} was varied, keeping Pp_{PV} at 1 and Pd_{PV} at 0, arbitrary chosen. Figure 8.9 (top) shows that the Pi_{PV} influenced the speed of the controller; the higher it is, the faster the SPP is reached. For a 1 minute reaction time of the controller, a Pi_{PV} of 8 appeared to be sufficient. Subsequently, the proportional parameter Pp_{PV} was varied, using $Pi_{PV} = 8$ and $Pd_{PV} = 0$. From Figure 8.9 (middle) it can be concluded that the proportional parameter has no influence on the control action. However, the standard deviation of the control signal increased with increasing Pp_{PV} and therefore it is safe to apply a value of $Pp_{PV} = 0$. Finally, using $Pi_{PV} = 8$ and $Pp_{PV} = 0$, the Pd_{PV} was varied, showing no influence on the control signal as well (Figure 8.9 bottom). However, again there was some influence on the standard deviation, so a value of $Pd_{PV} = 0$ was an optimal choice here.

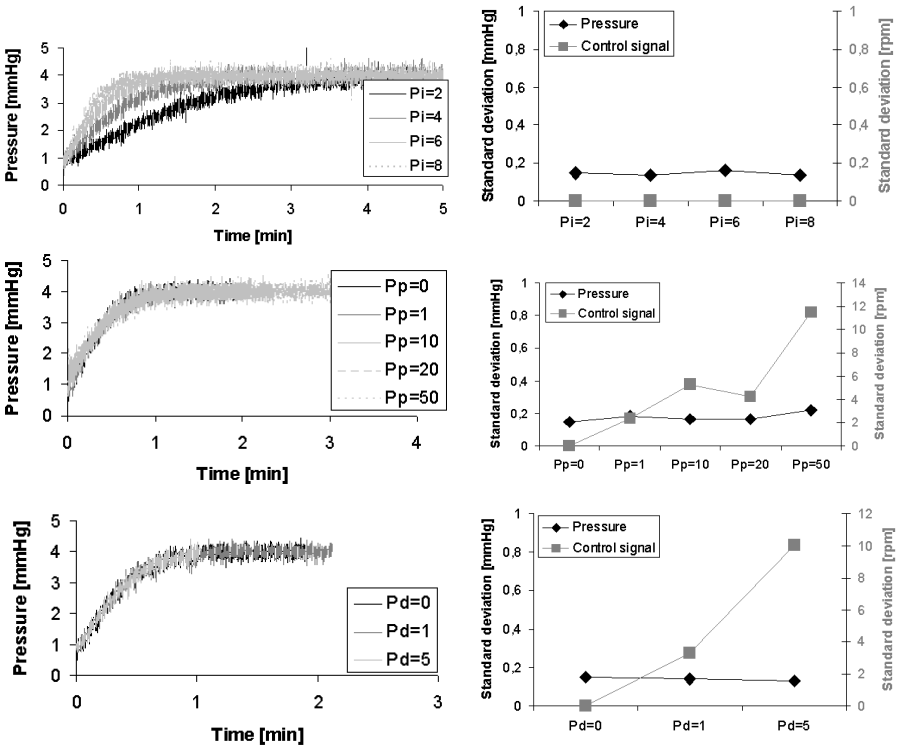

Figure 8.9: Influence of Pi_{PV} (top), Pp_{PV} (middle) and Pd_{PV} (bottom) variation of the controller on the perfusion pressure (left). On the right: standard deviation of the pressure [mmHg] and control signal [rpm]

Hepatic arterial control

The controller for the pulsatile pressure is separated in a controller that regulates the mean pressure and a controller that regulates the amplitude of the pulse. For the mean pressure controller, the SPP was set to 25 mmHg. Pi_{HA} variation was performed with $Pp_{HA} = 1$ and $Pd_{HA} = 0$.

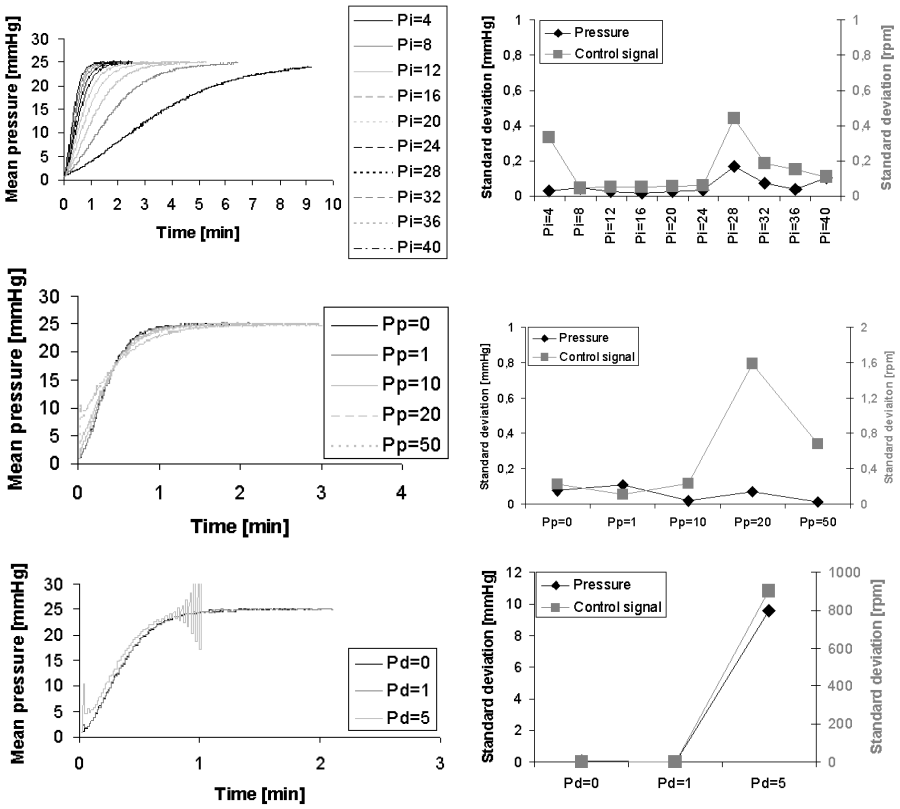

Figure 8.10: Influence of Pi_{HA} (top), Pp_{HA} (middle) and Pd_{HA} (bottom) variation of the controller on the perfusion pressure (left). On the right: standard deviation of the pressure [mmHg] and control signal [rpm]

According to Figure 8.10 (top), the optimal setting of Pi_{HA} to achieve a control reaction time of 1 minute was $Pi_{HA} = 40$, without invoking a large standard deviation. In addition, variation of Pp_{HA} was performed using $Pi_{HA} = 40$ and $Pd_{HA} = 0$ (Figure 8.10 middle). Figure 10 (middle) shows for $Pp_{HA} = 0$ to 20 comparable behavior, but if $Pp_{HA} = 50$ a clear overshoot is visible. This large step

in pressure is undesirable in the liver perfusion system, because it may damage the liver vessels. Since no clear difference between the other Pp_{HA} settings occurs and standard deviation was low, $Pp_{HA} = 0$ was optimal here. Third, the Pd_{HA} was varied, using $Pi_{HA} = 40$ and $Pp_{HA} = 0$ (Figure 8.10 bottom). Clearly, there is a large difference in controller behavior between $Pd_{HA} = 0$ or 1 and $Pd_{HA} = 5$. In the latter an undesirable overshoot is visible at the beginning, and an unstable oscillating behavior at the moment SPP is almost reached, which causes the increased standard deviation. Obviously, the controller did not work satisfactory at this point anymore. Since the behavior at $Pd_{HA} = 0$ is comparable with that at $Pd_{HA} = 1$, it was chosen here to take $Pd_{HA} = 0$.

In addition to the controller for the mean pressure, a separate controller for the amplitude of the pulsatile pressure was implemented. To find optimal settings here, first the Pi_{HAamp} was varied, keeping $Pp_{HAamp} = 1$ and $Pd_{HAamp} = 0$ (Figure 8.11 top).

Again, the influence of Pi_{HAamp} could be seen in the speed of the controller; with increasing values of Pi_{HAamp}, reaction time increased, visualized in increased slopes of the pressure amplitude signal (Figure 8.11 top). The optimal reaction time of 1 minute was reached by choosing $Pi_{HAamp} = 18$, keeping the standard deviation low. Using this value, in combination with $Pd_{HAamp} = 0$, the variation of Pp_{HAamp} resulted in Figure 8.11 (middle). Values of Pp_{HAamp} ranging from 0 to 20 show no large influence, but if $Pp_{HAamp} = 50$ there is an overshoot in the beginning, and an unstable signal afterwards. This could be clearly seen in the standard deviation as well. Since no clear difference between the lower values of Pp_{HAamp} could be seen, it was chosen here to take $Pp_{HAamp} = 0$. Finally, the Pd parameter is varied from 0 to 5, keeping $Pp_{HAamp} = 0$ and $Pi_{HAamp} = 18$ (Figure 8.11 bottom). Little difference could be found between $Pd_{HAamp} = 0$ and 1, but when $Pd_{HAamp} = 5$, oscillation occurred and the controller became unstable. Again, it proved to be sufficient to choose $Pd_{HAamp} = 0$.

In summary, it proved to be sufficient to include only an integral parameter (Pi) in the controller for the continuous perfusion as well as in the controllers for the mean and amplitude of the pulsatile perfusion (Table 8.2). The derivative (Pd) and the proportional parameter (Pp) appeared not to be beneficial to the control action. It must be mentioned that in the motor control unit (1-Q-EC, Maxon Motor, Sachseln, Switzerland) already a PI controller is build in to stabilize motor velocity.

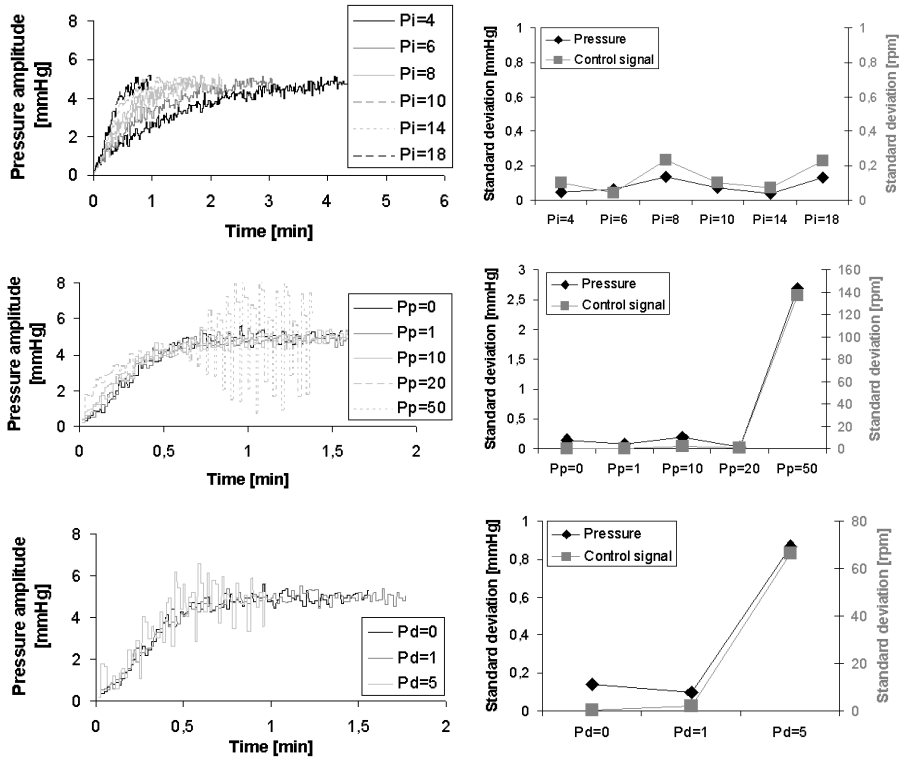

Figure 8.11: Influence of Pi_{HAamp} (top), Pp_{HAamp} (middle) and Pd_{HAamp} (bottom) variation of the controller on the perfusion pressure (left). On the right: standard deviation of the pressure [mmHg] and control signal [rpm]

	Portal Venous control	Hepatic Arterial control	
		Mean pressure	Pressure amplitude
Pp	0	0	0
Pi	8	40	18
Pd	0	0	0

Table 8.2: Optimal values of the PID parameters of the three controllers.

8.5.3 Testing

With the PID parameters set, as shown in Table 8.2, function of the controllers was tested using the set-up depicted in Figure 8.8. The SPP was set at 4 mmHg for the portal venous pump and mean and amplitude of the hepatic arterial pump were set at 25 mmHg and 5 mmHg, respectively. The variable resistance was changed from free flow to a total obstruction in 5 steps. For the portal venous pump this yielded a flow range from 675 to 0 ml/min (Figure 8.12), for the hepatic arterial pump a flow range from 450 to 0 ml/min (Figure 8.13).
Every increase in resistance after the portal venous pump resulted in a short pressure peak, which was regulated back to the SPP of 4 mmHg within one minute (Figure 8.12).

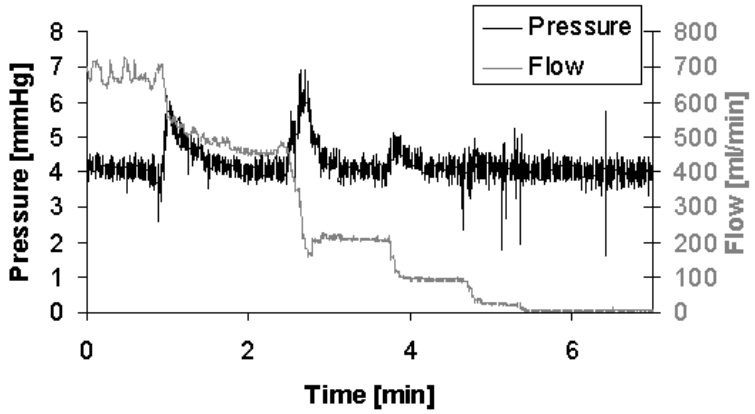

Figure 8.12: Portal venous control action during increasing resistance (SPP=4 mmHg).

Increases in resistance after the hepatic arterial pump resulted in pressure peaks as well. The mean pressure controller adjusted the control signal of the pump in such a way that the SPP of 25 mmHg was reached again with a response time of one minute (Figure 8.13 left).

During this increasing resistance after the hepatic arterial pump, pressure amplitude increased as well. Figure 8.12 (right) shows that the amplitude controller regulated the increased amplitude back to the SPP of 5 mmHg, again within a period of one minute.

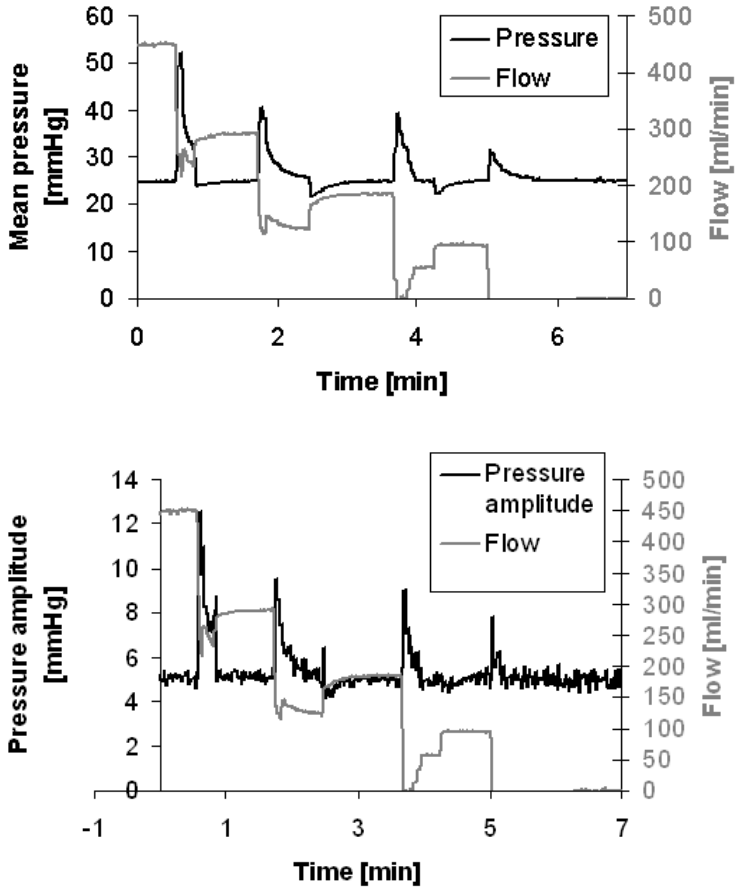

Figure 8.13: Hepatic arterial control action of the mean pressure (SPP=25 mmHg)(left) and pressure amplitude (SPP=5 mmHg)(right) during increasing resistance.

In conclusion, the three controllers complied with the specifications they were designed for, at the working pressures SPP_{PV} = 4 mmHg, SPP_{HAmean} = 25 mmHg and SPP_{HAamp} = 5 mmHg. Application in the Groningen HMP system is thereby justified. Additional measurements also showed that the three controllers worked satisfactory with SPP_{PV} = 2, 8 and 16 mmHg, SPP_{HAmean} = 12.5 and 50 mmHg and SPP_{HAamp} = 2.5 and 10 mmHg.

8.6 Design

The components mentioned in the preceding paragraphs of this chapter were incorporated in a state-of-the-art design of the Groningen HMP system. In accordance with Chapter 6, additional design requirements of the total system included portability, weighing less than 23 kg, userfriendlyness, compliance to standard surgical techniques, affordability and modularity.
The initial concept of the Groningen HMP system was based on the conventional cold storage, i.e. the liver is situated in an organ bag filled with UW-CS preservation solution which is placed in an cooling box filled with melting ice. This concept was maintained, with in addition a dual pumping system and an oxygenator. As mentioned earlier, the dual pump system contains a pulsatile and a continuous rotary pump (DeltaStream, MEDOS Medizintechnik, Stolberg, Germany), and operates with a controlled perfusion pressure. The perfusion pressure is measured at the entrances of the liver and compared to the set perfusion pressure by the controller which, subsequently, defines the speed of the electro-motor of the pumps. Parameter definition and read-out occurs at the interface, including set perfusion pressure, measured pressure, measured temperature and calculated flow. The prototype design of the HMP system was divided into a disposable section and an electro-mechanical section (Figure 8.14). The disposable section is situated totally inside the ice-filled cooling box, while the electro-mechanical section is placed outside the cooling box, on top of the lid.

8.6.1 Disposable section

The disposable section of the HMP system includes all sterile components and the polystyrene cooling box. It comprises the disposable pump heads, oxygenator, pressure sensors, temperature sensor, organ chamber and canulas and tubing.

The organ chamber consists of an airtight polycarbonate reservoir, in which the liver is situated, floating in the preservation solution. Connected to the organ

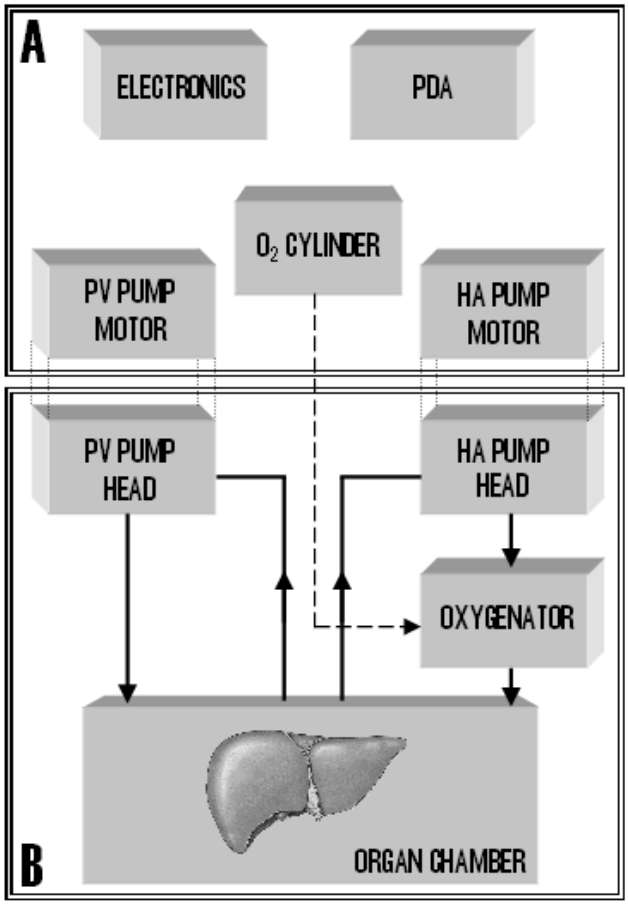

Figure 8.14: Components situation in the Groningen HMP system, divided into an electro-mechanical section (A) and a disposable section (B).The system includes a handheld computer (PDA), electronics, oxygen cylinder, portal (PV) and arterial (HA) pump, both divided into a pump motor and disposable pump head, oxygenator and organ chamber.

chamber are two suction tubes, leading the preservation solution to the pumps, and two perfusion tubes, directing the preservation solution via the canulas to the liver vessels.

8.6.2 Electro-mechanical section

The electro-mechanical section of the HMP system includes two electro-motors to drive the pump heads, an oxygen cylinder, an electronics unit, a handheld computer and a battery pack, all situated on the lid of the cooling box.
The oxygen cylinder is a carbon-fiber reinforced aluminium-lined cylinder (Hoek Loos, Eindhoven, The Netherlands, ZM 201H, 0.7 kg) containing 1 liter of 100% oxygen under 310 bar. This amount of oxygen is sufficient for 24 hours perfusion with an oxygen flow of 215 ml/min.
The electronics unit comprises two drivers for the pump motors (1-Q-EC Amplifier DEC 50/5, Maxon Motor ag, Sachseln, Switzerland), amplifiers for two pressure transducers and a temperature sensor, a circuit producing a sinusoidal power signal for the pulsatile hepatic arterial pump, an RS232 serial communication port and a power supply (12 Volt).
A handheld computer (iPAQ5550, Hewlett Packard, Utrecht, The Netherlands) with a data acquisition program (Labview 7.1, National Instruments, Austin Texas, USA) reads out and stores measured pressure and temperature signals, calculates perfusion flow and steers pump drivers and electronic circuit. The computer is supplied with a separate battery pack that enables a stand alone time of 24 hours.
At the working points of the pumps (4 mmHg, 300 ml/min and 30/20 mmHg, 100 ml/min for portal vein and hepatic artery, respectively) total energy consumption of the pump system was measured to be 0.5 Ampere at 12 Volts. For 24 hours of perfusion, this demands a battery pack with a capacity of 12 Ah at 12 V. A battery complying to these conditions was found in a military rechargeable Li-ion battery (UBI-2590, UltraLife batteries Inc, Newark NY, USA), weighting 1.4 kg.

8.6.3 Operating procedure

Combining the disposable and electro-mechanical sections results in an integrated design as shown in Figure 8.15. The sequence of assembly becomes clear from the exploded view depicted in Figure 8.16. During the organ procurement, the reservoir is filled with 4 liters of cold University of Wisconsin-Machine Preservation (UW-MP) solution. Subsequently, the total disposable unit (pump heads, oxygenator and tubing) is primed passively (under gravity) without inclusion of any

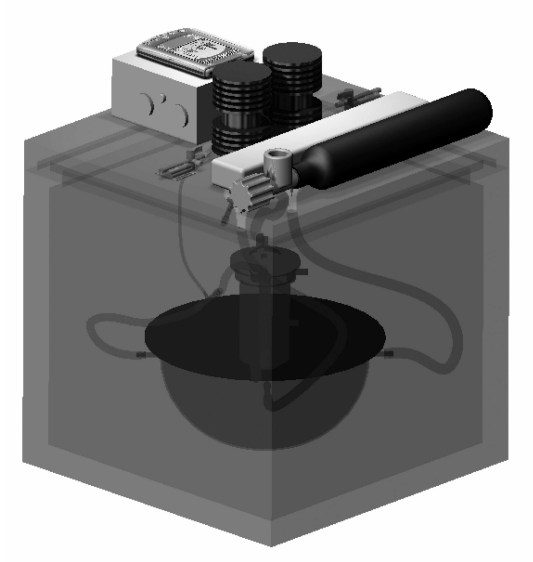

Figure 8.15: Prototype of the Groningen Hypothermic Liver Perfusion Pump with the disposable section situated inside the polystyrene cooling box and the electromechanical section situated on the lid.

Figure 8.16: Exploded view of the Groningen Hypothermic Liver Perfusion Pump.

air bubbles. After initial wash-out of blood from the liver, cannulas are inserted into portal vein and hepatic artery. The organ is placed in the reservoir and the cannulas are fixed to the portal and arterial line, respectively. The reservoir lid is closed and at this point, sterility of the liver and perfusate is guaranteed. The disposable unit is placed into the cooling box and surrounded by ice. The connection between the pump heads and the pump motors, via a bore in the lid, can be made. Pressure sensors are connected to the pressure lines and motors, pressure and temperature sensors are plugged into the electronics unit. At this point, the perfusion pump is operational, and machine preservation time starts. The entire procedure is depicted in Figure 8.17.

8.6.4 Special features

The prototype of the Groningen Hypothermic Liver Perfusion Pump with the separation between disposable and electro-mechanical unit and a number of specific design details introduces additional and special features that could facilitate future developments in machine perfusion.

1. The reservoir of the HMP system consists of a bowl containing preservation solution. The organ is placed into the reservoir and is entirely submerged in the solution. The reservoir is surrounded by ice and the cooling box, maintaining a solution temperature around 0°C. To this conventional cold storage preservation procedure, we added the two pump systems. This specific feature, the fully submerged organ in cold preservation solution, allows that, in case of absence of perfusion, caused by e.g. power failure or pump failure, the organ is still preserved using the static cold storage method. Commercially available kidney perfusion machines (e.g. GAMBRO, Waters, see chapter 6) work by cooling with either a Peltier-element or heat exchanger and a 'dry' organ chamber in combination with a separate reservoir. In case of a power failure, the cooling devices stop working, perfusion stops and the organ dries up. The Groningen HMP system, with the disposable fluid-filled unit situated totally in the ice-filled cooling box counteracts that problem. In case of failure, machine perfusion is simply automatically substituted by static cold storage.

2. Recently, research in organ preservation of predominantly non-heart-beating donor organs has led to new insights in optimal preservation temperature. Conventional hypothermic preservation with an acellular preservation solution causes hypothermia-induced cellular injury and osmotic imbalances.

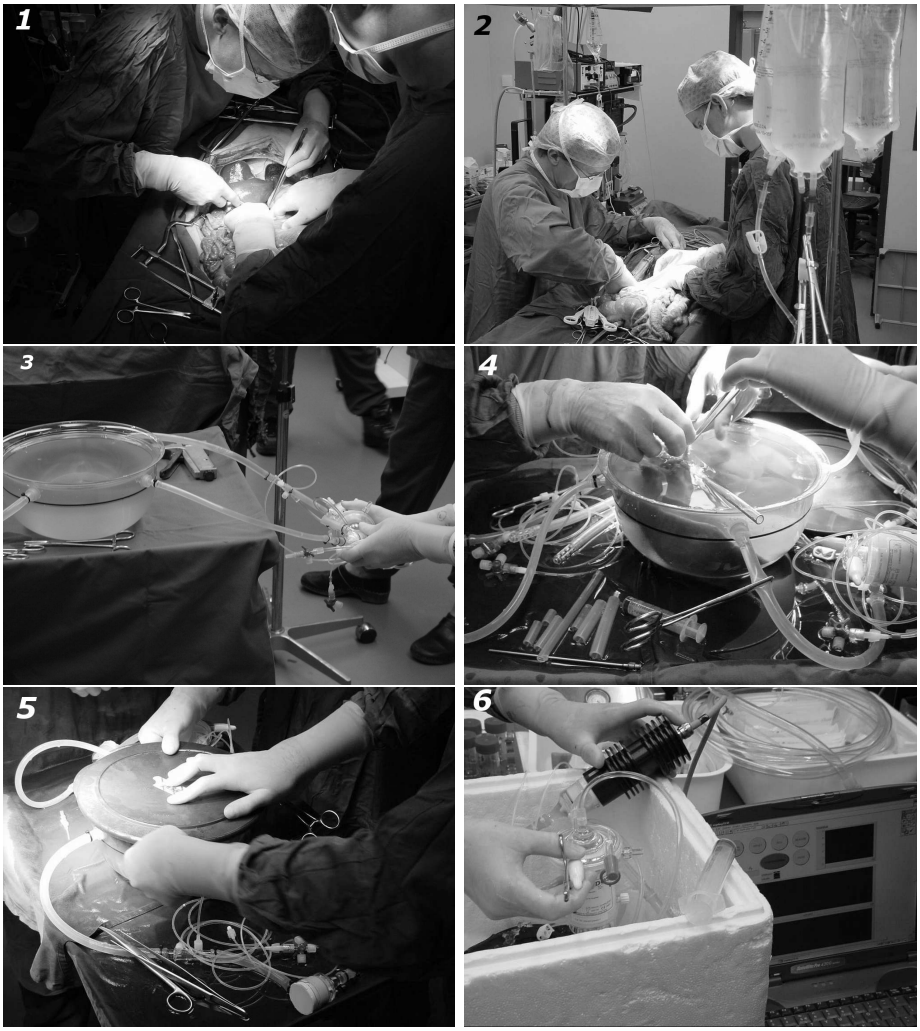

Figure 8.17: Operating procedure of the Groningen HMP system. 1 liver procurement, 2 initial flush, 3 priming disposable module, 4 connecting canulas, 5 sealing disposable module, 6 connecting pump motors and start perfusion.

Preservation of the organ at body temperature maintains normal metabolism and minimizes the accumulation of cell damaging substrates during storage. Therefore, normothermic preservation may lead to better preservation outcome, and furthermore it allows to assess viability during preservation, since the organ is fully functioning. However, preservation at normothermic temperature is complex and induces additional difficulties as well. Besides the necessity to include whole blood, packed red blood cells or for example perfluorcarbons as oxygen carriers, temperature has to be actively maintained at body temperature, including the addition of nutrients.
In the Groningen HMP system, the oxygenator is supplied with a build-in heat exchanger which is able to heat the preservation solution to any arbitrary temperature. As a consequence, an extra heat pump and medium can be included. In combination with the excellent isolation characteristics of the cooling box, the HMP system has the potential to work in the future also as an NMP (normothermic machine perfusion) system. The selection of disposable components, which are all already in use in heart-lung machine procedures, ensures furthermore the ability to use blood or blood components in NMP.

3. The electro-mechanical components are situated in the lid of the cooling box by means of a rack construction (not shown). This design feature allows the electro-mechanical section to be placed on every arbitrary cooling box lid. The only prerequisite is that the lid of the cooling box needs two bores to connect the pump heads to the motors. The prototype was designed around a polystyrene cooling box (300x300x305 mm, Wolters Kunststoffen, Enter, The Netherlands), but it is conceivable to use other dimensions or even design a fully integrated special cooling box around the electro-mechanical and disposable units.
   This special modular design makes it possible to also use the Groningen HMP system for kidney perfusion, by retaining the pulsatile pump and omiting the continuous pump (Figure 8.18), or using both pumps in a pulsatile manner.

4. As mentioned earlier, the Groningen HMP system was designed in such a way that the conventional static cold storage procedure is extended with a dual pump system and the necessary controls. Static cold storage comprises the ice-filled cooling box and the reservoir containing liver and 4 liters of preservation solution. Added to that are the remaining disposable components and the electro-mechanical unit. This amounts to a total additional

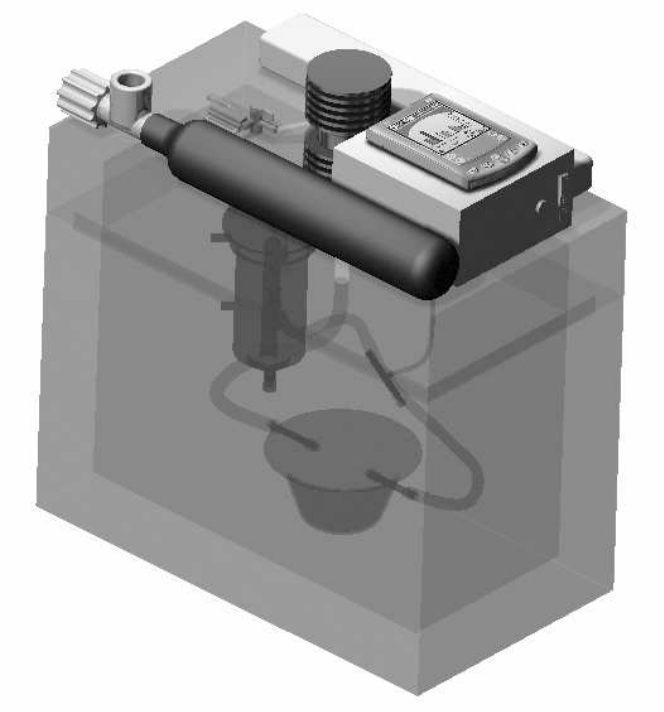

Figure 8.18: Prototype of the Groningen HMP system configured for kidney preservation.

Component	Weight [kg]		
	CS	HMP	
cooling box	0.5		
UW-MP	4		(4 liter)
reservoir	0.3		
ice	7.2		(15 liter)
pump head (2×)		0.2	(2×0.1)
pump motor (2×)		1.9	(2×0.95)
oxygenator		0.2	
oxygen cylinder		0.7	
electronics		0.7	
battery		1.4	
handheld computer		0.2	
Total	12	5.3	= ***17.3 kg***

Table 8.3: Additional weight of the Groningen HMP system compared to static cold storage (CS).

weight compared to static CS of 5.3 kg (Table 8.3). The total weight of the complete HMP system prototype is thus 17.3 kg which complies to the design criterium of a weight below 23 kg.

8.7 References

1. Fujita S, I Hamamoto, K Nakamura, K Tanaka, K Ozawa. Evaluation of oxygen necessity during hypothermic liver perfusion. Arch Jpn Chir 1993; 62(5): 228-40.

2. Hart 't NA, A van der Plaats, HGD Leuvenink, H van Goor, GJ Verkerke, G Rakhorst, RJ Ploeg, Hypothermic machine perfusion of the liver and the critical balance between perfusion pressures and endothelial injury, Transplant Proceedings 2005; 37: 332-334.

3. Orloff MS, AI Reed, E Erturk, RA Kruk, SA Paprocki, SC Cimbalo, GJ Cerilli. Nonheartbeating cadaveric organ donation. Ann Surg 1994; 220(4): 578-585.

4. Polyak MMR, BO Arrington, WT Stubenbord, J Boykin, T Brown, MA Jean-Jacques, J Estevez, S Kapur, M Kinkhabwala. The influence of pulsatile

preservation on renal transplantation in the 1990s. Transplantation 2000; 69(2): 249-58.

5. van der Plaats A, NA 't Hart, AM Morariu, GJ Verkerke, HGD Leuvenink, RJ Ploeg, G Rakhorst. Effect of University of Wisconsin solution on hemorheology in organ preservation. Transpl Int 2004; 17: 227-30.

6. Waters TR, V Putz-Anderson, A Garg. Applications manual for the revised NIOSH lifting equation, US department of health and human services. Public health service, Cincinnati O, USA, 1994